Response to the section 112, 2nd paragraph rejections

Claims 11, 18, and 28 are rejected under 35 U.S.C. 112, 2nd paragraph for various errors noted by the Examiner. The dependency of claim 11, the preamble of claim 18, and the typographic error in claim 28 have been corrected, which should obviate the clarity rejections of these claims.

Claims 1-28 are rejected as allegedly unclear for reciting the phrase "strong promoter." As discussed below, one skilled in the art would recognize that the phrase "strong promoter" refers to a promoter which initiates the persistent, repeated transcription of RNA.

The Examiner asserts that "strong" is a relative term whose metes and bounds are uncertain, and that the specification does not provide a standard for ascertaining the requisite degree promoter activity. Applicant respectfully disagrees.

M.P.E.P. §2173.05(b) states that:

> The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co. v. Industrial Crating & Packaging, Inc.*, 731 F.2d 818, 221, USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.

A relative term is definite if it can be interpreted by some standard presented in the specification. Alternatively, a relative term is considered definite if "one of ordinary skill in the art, in view of the prior art and the status of the art, would nevertheless be reasonably apprised of the scope of the invention." M.P.E.P. §2173.05(b). Here, one of ordinary skill in the art is reasonably apprised of the invention's scope through the usage of the phrase "strong promoter" in the specification and in the prior art.

For example, in Glick BR et al. (1998), Molecular Biotechnology: Principles and Applications of Recombinant DNA, ASM Press, Washington, DC, pg. 110 (attached), defines a strong promoter as "one that has a high affinity for RNA polymerase, with the

consequence that the adjacent downstream region is highly (frequently) translated[1]." This definition is consistent with the immunology patent literature; see, *e.g.*, U.S. Pat. No. 4,973,551 to Condra, titled "Vector for the Expression of Fusion Proteins and Protein Immunogens" (attached), which states at col. 7, lns. 29-41 that (emphasis added):

> An appropriately constructed expression vector should contain: an origin of replication for autonomous replication in host cells, selective markers, a limited number of useful restriction enzyme sites, a high copy number, and strong promoters. A promoter is defined as a DNA sequence that directs RNA polymerase to bind to DNA and to initiate RNA synthesis. *A strong promoter is one which causes mRNAs to be initiated at high frequency.* Expression vectors may include, but are not limited to, cloning vectors, modified cloning vectors, specifically designed plasmids or viruses.

The usage of the term "strong promoter" in the present specification and claims is consistent with the art-recognized definition of a promoter which produces persistent, repeated initiation of RNA transcription. See, *e.g.*, pg. 26, lns 12-14 and pg. 38, lns. 6-7 of the present specification, which states "[t]he transgene should be expressed to very high levels in the transfectants . . . [t]hus, the construct should contain a strong promoter" and "[g]enerally speaking, a 'strong' promoter is a promoter which achieves constitutively high expression of the dCTG in the transfected cells."

In view of the present specification and the prior art usage as discussed above, one of ordinary skill in the art would readily understand the definition and scope of "strong promoter" as recited in the present claims. Applicants respectfully request that the 35 U.S.C. 112, 2nd paragraph rejection of claims 1-28 be withdrawn.

Response to section 112, 1st paragraph rejections

Claims 1-28 are rejected under 35 U.S.C. 112, 1st paragraph as allegedly non-enabled for the use of any cognate proto-oncogene transgenes, other than c-src527, v-src and c-src, to construct the claimed cellular immunogens. Applicants respectfully disagree.

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[1] Webster's 9th Collegiate Dictionary (1987), Merriam Webster, Inc, Springfield MA, defines "frequent" as "happening at short intervals; often repeated or recurring; habitual, persistent."

A specification which discloses how to make and use a claimed invention is presumed to comply with the first paragraph of 35 U.S.C.112, unless there is a reason to doubt the objective truth of the specification. In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). The initial burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the examiner. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Thorpe, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985); In re Piasecki, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984). Here, the present specification clearly discloses how to make and use the claimed cellular immunogens, and the Examiner has failed to rebut the assertions made therein.

The claims recite transgene constructs comprising at least one transgene cognate to the target proto-oncogene, and a strong promoter to drive the expression of the cognate transgene in the transfected cells. The claimed transgene encodes a gene product which induces immunoreactivity to host self-determinants of the target proto-oncogene gene product. This is a specific class of proto-oncogene transgene constructs which can be readily determined by one of ordinary skill in the art from the teachings of the specification.

An extensive list of proto-oncogenes for which cognates can be found is presented in Table 1. The specification also provides ample guidance on how to choose or engineer cognate proto-oncogenes, beginning on page 26 with the section entitled "Selection of Cognate Transgene for Preparation of Cellular Immunogen," and continuing through page 35. This passage includes instructions on how to screen for cognate transgenes with available computer sequence alignment programs (see pgs. 27-28 of the present specification), and how to test for an immune response induced by immunogens made with the cognate transgenes via the "delayed hypersensitivity reaction" skin test, which is a simple physiological assay (see pg. 29, lns. 13-30 of the present specification).

The delayed hypersensitivity reaction skin test allows one skilled in the art to confirm the presence of an immune response to the cognate transgene product from the cellular immunogen. (A positive reaction indicates the cellular immunogen has been recognized by the subject's immune system.) Once an immune response to the cognate product has been confirmed, the subject can then be tested for an immune response to the *self* proto-oncogene product, again with a delayed hypersensitivity skin test. A positive response to this second skin test means that the cognate proto-oncogene transgene carried in

the cellular immunogen has elicited an immune response to the *self* determinant of the endogenous proto-oncogene product. A transgene that does not elicit a response to the second skin test is not a transgene encoding "a gene product which induces host immunoreactivity to host self-determinants of the product of the target proto-oncogene gene," as required by the claims (see pg. 43, lns. 8-28 of the present specification).

Page 38, lns. 1-11 and Examples 1.A and 3.B of the present specification discuss how to make the cognate transgene expression vectors. As expression vector engineering is well-known in the art, detailed descriptions of the vector construction need not (indeed, should not) be repeated in the present specification. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). *See also* In re Wands, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) ("A patent need not disclose what is well-known in the art."); Spectra-Physics, Inc. v. Coherent, Inc., 3 U.S.P.Q.2d 1737, 1743 (Fed. Cir. 1987), cert. denied, 108 S.Ct. 346 (1987) ("A patent need not teach, and preferably omits, what is well-known in the art."); Webster Loom v. Higgins, 105 U.S. 580 (1981) (The specification may assume "that which is common and well-known" to persons skilled in the relevant art). See also M.P.E.P. 601[2]. The need for a strong promoter and how to identify appropriate cognate transgenes for insertion into the vector is also disclosed (see pg. 38, lns. 5-6 of the present specification). It is therefore within the ability of one of ordinary skill in the art to choose an appropriate cognate transgene based on the teachings of the specification, and use the transgene to construct an expression vector.

Page 39, ln. 16 to pg. 41, ln. 15 of the present specification discloses suitable methods for transfection of cell with the cognate transgene expression vectors, such as the DEAE-dextran or calcium phosphate methods, or by cationic phospholipid delivery. As such methods are well-known in the art, detailed descriptions of the methods need not be disclosed. Hybritech, Inc. v. Monoclonal Antibodies, Inc., *supra*. Regarding the dosage of transfected cells to be used in the claimed vaccination methods, the specification at page 42, lns. 26-28 discloses that "[a]s a general rule, it is desirable to generate the strongest immune

[2] M.P.E.P. 601 provides, under "Arrangement and Content of the Specification," part H: "Where . . . processes which are conventional and generally widely known in the field to which the invention pertains, form a part of the invention described and their exact nature and type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail."

response consistent with clinical monitoring of no adverse side effects," and suggests multiple rounds of inoculation with 10^7 cells per round. The existence and strength of the immune response induced by the immunogen can be monitored by a standard delayed hypersensitivity skin test, as discussed above (see pg. 43, lns. 4-6 of the specification).

Contrary to the Examiner's assertions, selection of a cognate transgene, construction of a cellular immunogen, and use of the delayed hypersensitivity skin test to screen for cellular immunogens falling within the scope of the claims do not constitute "undue experimentation." In the "unpredictable" arts, such as chemistry and biotechnology, some experimentation may be required to identify compounds and methods which fall within the scope of the claims. As long as the experimentation does not "require ingenuity beyond that to be expected of one of ordinary skill in the art," the experimentation will not be undue. In re Angstadt, 190 USPQ 214, 218 (CCPA 1976), citing Fields v. Conover, 170 USPQ 276, 279 (1971).

In Angstadt, the patent in suit disclosed a complex catalyst comprising a hexaalkylphosphoramide and a transition metal salt to catalyze the oxidation of secondary or tertiary alkylaromatic hydrocarbons to form hydroperoxides. An exemplary list of transition metal salt catalysts was provided, as well as a description of how to test a putative complex catalyst. The patent also described a finite result (the formation of hydroperoxides) as the signal that a putative complex catalyst fell within the scope of the claims. The Federal Circuit held that:

> "If one skilled in this art wished to make and use a transition metal salt other than those disclosed in appellants' 40 runs, he would merely read appellants' specification for directions how to make and use the catalyst complex to oxidize the alkylaromatic hydrocarbons, and could then determine whether hydroperoxides are, in fact, formed. The process discovered by appellants is not complicated, and there is no indication that special equipment or unusual reaction conditions must be provided when practicing the invention."

In re Angstadt at 218. Thus, if the disclosed process is not complicated to those of ordinary skill in the art, and no unusual or reaction conditions or special equipment is required, then simply following a patent disclosure to determine if a compound falls within the scope of the claims does not constitute undue experimentation.

Here, an exemplary list of cognate proto-oncogenes for which cognate transgenes can be found is provided in Table 1. Table 2 provides a further list of cognate transgenes that carry a deletion mutation to render them not-transforming. As discussed above, the specification provides ample teaching to those skilled in the art on how to select a cognate transgene, construct an expression vector, and transfect cells with it to create a cellular immunogen. A well known, simple, rapid and effective technique (the delayed hypersensitivity skin test) is disclosed as a way to determine whether a putative cellular immunogen falls within the scope of the claims. The amount of experimentation required to find a cognate transgene does not, therefore, "require ingenuity beyond that to be expected of one of ordinary skill in the art," and is not undue. Cognate transgenes which do not produce cellular immunogens of the invention "will readily be discovered and, of course, nobody will use them and the claims do not cover them." In re Angstadt at 219. Thus, the specification fully describes to one skilled in the art how to make and use the claimed cellular immunogens without undue experimentation.

The Examiner alleges that the teachings of Reilly et al. (2000), *Cancer Res.* 60: 3569-3576 ("Reilly") rebut the presumption that applicants' disclosure complies with 35 U.S.C. 112, 1st paragraph. According to the Examiner, Reilly allegedly shows that the activity of cellular immunogens is unpredictable, and that one of ordinary skill in the art would therefore be unable to practice the scope of the invention as claimed. Detailed Action, paragraph bridging pgs. 4-5. The Applicants disagree with the Examiner's interpretation of Reilly.

Reilly discloses HER-2/*neu* transgenic mice which develop spontaneous focal mammary adenocarcinomas. Cell lines derived from these tumors are highly immunogenic in the parental mouse strain, but are considerably less immunogenic in the Her2/*neu*. transgenic mice. Nevertheless, Reilly states that "it is possible to immunize neu-specific T cells to achieve neu-specific tumor rejection *in vivo*" in the transgenic mouse. See Reilly, abstract. Thus, rather than indicating unpredictability in the art, Reilly appear to demonstrate that anti-Her2/*neu* immunization is a promising approach to cancer immunotherapy.

Also, the Her2/*neu* tolerance seen in the transgenic mouse of Reilly is likely due to the expression, during embryogenesis or shortly thereafter, of the Her2/*neu* transgene in one

or more tissues. The induction of tolerance to the transgene in the Reilly transgenic mouse does not imply that tolerance would be induced to the product of the naturally occurring transgene homologue, which is present in the genome of the non-transgenic parental strain. In fact, little or no tolerance would likely be imposed by the naturally present germ-line Her2/*neu* homologue in a non-transgenic mouse, as shown by strong immunity against Her2/*neu* tumors seen in the Reilly parental mouse strain. Thus, the tolerance seen in the Reilly transgenic mouse does not show that the activity of the claimed cellular immunogens is unpredictable.

The prior art provides additional evidence that naturally-occurring germ-line Her2/*neu* does not impose a tolerance that precludes an effective immune response; for example, Disis et al (1994), *Cancer Res.* 54: 16-20 (of record; see Ref. AW in the IDS filed July 5, 2001) reported that some patients who present with Her2/*neu*-positive breast carcinomas show antibody and T cell reactivity to the Her2/*neu*-encoded product.

The Examiner further states on pg. 5 of the Detailed Action that Reilly "disclose(s) that work still needs to be done in order to determine vaccine efficacy," implying that the presently claimed cellular immunogens also allegedly lack efficacy. However, taken in context, this disclosure from Reilly clearly relates to immunity in the Her2/*neu* transgenic mouse; see the last paragraph in the Discussion section on pg. 3575 of Reilly:

> Additional work is required to determine whether the level of transgene expression influences the extent of tolerance to neu, or whether lactational status has an effect on vaccine-mediated antitumor immunity. Furthermore, now that it is clear that neu-specific antitumor immunity can be induced in neu-N (*i.e.*, transgenic) mice despite tolerance, the next step is to determine what steps are necessary for the improvement of vaccine efficacy.

Thus, Reilly in fact teaches that an immune response can be elicited in the parental and (despite the tolerance) in the transgenic mice. The present claims do not require any particular efficacy for the cellular immunogens, only that the immunogens elicit an immune response in the host against the target proto-oncogene. Thus, far from showing that vaccination with the claimed immunogens is unpredictable, Reilly supports the enablement

of the present claims. The teachings of Reilly are therefore insufficient to rebut the presumption that Applicants' disclosure complies with section 112, 1st paragraph.

Finally, the Examiner states that the absence of working examples involving transgenes other than c-src527, v-src or c-src indicates a lack of guidance on how to make or use the claimed cellular immunogens with other transgenes. Detailed Action, pg. 5.

There is no requirement that the working examples provide the entire scope of enablement needed to support a claimed invention. Rather, the specification *taken as a whole* must be enabling. In re Barr, 170 USPQ 330 (CCPA 1971). As discussed above, the present specification contains ample direction on how to choose a cognate proto-oncogene and insert it into an expression vector, construct a cellular immunogen and determine whether the cellular immunogen is capable of evoking an immune response to host self-determinants of over-expressed proto-oncogenes. The specification is thus presumed enabling for the full scope of the claims as written, a presumption which stands un-rebutted by the Examiner. The working examples are simply specific illustrations of the claimed invention, which are expressly identified as non-limiting (see pg. 44, lns.1-2 of the present specification).

Thus, the present specification is enabling for cellular immunogens constructed with any cognate transgene, and the 35 U.S.C. 112, 1st paragraph rejection of claims 1-28 should be withdrawn.

Claims 19-28 are rejected under 35 U.S.C. 112, 1st paragraph, because the specification allegedly does not enable a method of generating protective immunity in a subject by vaccination with the claimed cellular immunogens. (The Examiner acknowledges that the therapeutic anti-tumor immunity can be generated with the claimed cellular immunogens; see pg. 6 of the Detailed Action.) The Applicants respectfully traverse the rejection.

As discussed above, the Applicants enjoy a presumption that the claims comply with the first paragraph of 35 U.S.C.112, unless there is a reason to doubt the objective truth of the teachings in the specification. In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). The Examiner may challenge this presumption with evidence or cogent reasoning inconsistent with the specification. In re Strahilevitz, 212 USPQ 561 (CCPA 1975); In re

Bowen, 181 USPQ 48 (CCPA 1947); In re Marzocchi, 169 USPQ 367 (CCPA 1971). Here, the Examiner has not provided sufficient evidence or reasoning that one skilled in the art would doubt that the claimed immunogens produce an immunoprophylactic effect.

Vaccination or immunization, as understood by one skilled in the art, does not require a total prevention of disease in an immunized subject. Sztein and Mitchell characterize "immunoprophylactic vaccination" as the "ability to 'recall' previous exposure to antigens and respond rapidly with immunological effector responses of increased magnitude (immunological memory)," and that this "constitutes the foundation of immunoprophylactic vaccination against infectious agents." See page 100, 1st paragraph of section B in Sztein and Mitchell, Recent Advances in Immunology: Impact on Vaccine Development, in New Generation Vaccines 2nd Ed., 1997, (Levine, Woodrow, Kaper, and Cobon, eds.), pp 99-125 (attached). One of ordinary skill in the art would therefore understand that a vaccine-induced immune response, which results in less than complete immunoprophylaxis, qualifies as an "immunization" or "vaccination" if memory activation of the immune system is demonstrated.

Here, the claimed cellular immunogens cause memory activation of the immune system, as demonstrated by the delayed hypersensitivity skin test described on pg. 29 of the present specification. See also Black (1999), *Dermatology Online J.* 5: 7 (attached, abstract only), which states "(the delayed type hypersensitivity) reaction has been shown to be absolutely dependent on the presence of memory T-cells." One skilled in the art would therefore consider the immune response induced by the claimed immunogens to have both therapeutic and prophylactic effects.

The Examiner states on pg. 6 of the Detailed Action that no working examples are provided which teach how to elicit protective immunity. However, there is no requirement that the working examples provide the entire scope of enablement needed to support a claimed invention. In re Barr, 170 USPQ 330 (CCPA 1971). In any case, at least Example 1 indicates that an immunoprophylactic response can be achieved with the claimed immunogens.

The studies disclosed in Example 1 were performed on a line of histocompatible chickens, for which expression of v-src induces the formation of regressor tumors and expression of c-src527 induces formation of progressor tumors. The difference in v-src and

c-src527 tumor growth in these chickens is due to the much greater immunogenicity of the v-src- versus the c-src527-encoded product, which correlates to the differing degrees of "selfness" exhibited by the two products. The v-src product differs from the endogenous c-src product by a number of substitutions, whereas the c-src527 product differs from endogenous c-src by only one amino acid substitution in the carboxy terminus.

The priming achieved by v-src DNA inoculation (*i.e.*, the induction of regressor tumor growth) exerts a significant protective effect against progressor tumor growth from c-src527 inoculation. As the C-termini of the v-src and c-src527 products have no sequence homology, induction of an immune response to c-src527 by v-src could not have been directed to the c-src527 mutation, but only to the parts of the molecule identical to the endogenous c-src. Thus, the experiments in Example 1 are tantamount to showing that expression of a cognate gene (v-src) presented as an antigen in tumor cells can result in induction of a protective immune response to a self-determinant (c-src) from tumor cells.

The Examiner relies on Yoshizawa et al. (2001), *Arch. Immunol. Ther. Exp. (Warz)* 49: 337-343 ("Yoshizawa"; abstract only) and Evans et al. (1999), *Q. J. Med.* 92: 299-307 ("Evans") rebut the assertions of the specification, by alleging that these references show prophylactic vaccination with cellular immunogens is unpredictable. Applicants disagree with the Examiner's interpretation of these references.

Yoshizawa discusses the enhancement of immunogenicity using cellular immunogens modified to express certain tumor antigens; *i.e.*, an antigen defined by a cancer-specific mutation. However, as disclosed on pg. 12, lns. 3-11 of the present specification, "the present invention is not based on the immune recognition of a determinant defined by a cancer specific mutation." Rather, the claimed vaccination methods rely on generating an immune response to self antigens by using "the high degree of primary sequence homology that exists between the protein product of a targeted proto-oncogene and that of its cognate . . ." Furthermore, the cellular immunogens of Yoshizawa appear to derive from normal or neoplastic cells that are syngeneic (*i.e.*, from the same inbred mouse strain) or autologous (*i.e.*, from the same individual); regardless, there is no specific mention that the immunogens are produced from allogeneic cells. As the present cellular immunogens are not based on immune recognition of tumor specific mutations, and

are produced from allogeneic cells, the relevance of Yoshizawa to the claimed methods is not apparent.

Evans reviews various cancer vaccines which have proposed or tested for the generation of an anti-tumor immune response. The Examiner misquotes Evans as stating that immunoprophylactic immunization with cellular immunogens "belongs in the realm of fiction." See pg. 6 of the Detailed Action. However, Evans actually states on pg. 303, 2nd col. that "[t]he notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs in the realm of fiction," and indeed the lead sentence of this paragraph states the "[t]he notion that the immune system can be activated by cancer vaccines to attack and reject established tumors is a fact." Thus, Evans actually tells one skilled in the art that the ability of cancer vaccines to elicit an anti-tumor immune response is not unpredictable, but is rather a fact.

Moreover, Evans discloses that cellular immunogens based on allogeneic tumor cell lines have "the advantage of being more practical for use in clinical practice . . . and may also amplify the immune response." Evans therefore supports, rather than rebuts, the assertions of the present specification.

The present specification fully describes methods of generating therapeutic or protective immunity in a subject with the claimed cellular immunogens, and the Examiner has failed to provide evidence or cogent reasoning that one of ordinary skill in the art would doubt the objective truth of the specification. The 35 U.S.C. 112, 1st paragraph rejection of claims 19-28 is therefore improper, and should be withdrawn.

Response to the nonstatutory double patenting rejection

Claims 1-18 are rejected as allegedly not being patentably distinct from claims 1-16 of U.S. Pat. No. 6,365,151 (the "'151 patent"). Applicants respectfully disagree.

The cellular immunogens are made from *allogeneic* cells, whereas those of the '151 patent are made from *autologous* cells. The present specification at pg. 15, lns. 1-11 distinguishes these two types of vaccine strategies as follows:

> We have described a similar vaccination strategy in PCT/US97/00582[3]. However, the methodology described therein utilizes excised host cells for preparing the cellular immunogen. According to the present invention, the cellular immunogen is prepared from cells obtained from a donor other than the patient, and other than an identical twin of the patient. Hence, while PCT/US97/00582 describes an inoculation constituting a syngeneic transfer, the present invention relies upon an allogeneic transfer. Given the outbredness of the human population, there will inevitably be allelic differences between the donor and the patient. These differences do not impede the induction of immunity to the cognate proto-oncogene encoded product overexpressed in the allogeneic transfectants used as immunogen.

By definition, allogeneic cells express different MHC class I alleles from the subject's cells (including tumor cells that may be present). The "foreign" (*i.e.*, allogeneic) class I MHC molecules expressed by the allogeneic cellular immunogens elicit a stronger antigenicity than autologous cellular immunogens. For this reason, one skilled in the art would expect cellular immunogens made from autologous cells to be less effective than those made from allogeneic cells. This notion is supported by Evans, which teaches that allogeneic tumor cell lines would amplify the immune response as compared to autologous tumor cells (see Evans, pg. 301, 2nd col.). The use of allogeneic cells to produce cellular immunogens is therefore not taught or suggested by the disclosure of the '151 patent, and the double-patenting rejection of claims 1-18 over this patent should be withdrawn.

Response to section 102(b) rejection

Claims 1, 2, 4, 8, 9, 11, 13 and 17-18 are rejected as allegedly being anticipated under 35 U.S.C. 102(b) by Ramsay et al. (1990), *P.N.A.S. USA* 87: 2102-2106 ("Ramsay"). Applicants respectfully traverse the rejection.

Under 35 U.S.C. 102, every limitation of claim must identically appear in a single prior art reference for it to anticipate the claim. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Absence from the reference of any claim element negates anticipation. Kloster Speedsteel AB v. Crucible, Inc., 230USPQ 81, 84 (Fed. Cir. 1986). Ramsay discloses the neoplastic transformation of avian cells with human and retroviral MYC sequences. The

[3] This is the International counterpart of the '151 patent.

human and retroviral MYC sequences in Ramsay must therefore be transforming. The transformed cells themselves, of course, exhibit the uncontrolled growth characteristic of neoplastic cells.

The claims as amended recite that the cognate transgenes used to construct the cellular immunogens are non-transforming, or that the transfected donor cells are non-dividing. Ramsay therefore does not anticipate claims 1, 2, 4, 8, 9, 11, 13 and 17-18, and the 35 U.S.C. 102(b) rejection over this reference should be withdrawn.

New claim 29 recites cellular immunogens made with vectors comprising wildtype AKT-2, c erbB-2, mdm-2, c-myb, c-src, c-ras and c-yes cognate proto-oncogenes. Ramsay does not disclose cells transfected with these particular wildtype proto-oncogenes, and therefore does not anticipate this claim. Moreover, the studies in Ramsay are designed to test the potency of neoplastic transformation by human MYC sequences (see Ramsay, abstract and pg. 2102, 1st col.). Ramsay does not teach or suggest the production of allogeneic cellular immunogens with a cognate proto-oncogene, where the host is immunized against the effects of a target proto-oncogene. This reference therefore does not render new claim 29 (and its and its dependent claims 30-33) obvious.

Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

MICHAEL S. HALPERN *et al.*

BY: _____

DANIEL A. MONACO
Registration No. 30,480
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
Tel: 215-988-3309
Fax: 215-988-2757
Attorney for Applicants

Appendix A – "Marked-up" Version of Amended Claims as Required Under 37 C.F.R. 1.121(c)(1)(ii)

1. (once amended) A cellular immunogen for immunizing a host against the effects of the product of a target proto-oncogene, the overexpression of which target proto-oncogene is associated with a cancer, which cellular immunogen comprises allogeneic donor cells which have been transfected with at least one transgene construct comprising at least one transgene cognate to the target proto-oncogene and a strong promoter to drive the expression of the transgene in the transfected cells, wherein the transgene is nontransforming and encodes [encoding] a gene product which induces host immunoreactivity to host self-determinants of the product of the target proto-oncogene gene.

2. (once amended) An immunogen according to claim 1 wherein the transgene comprises:

(1) [wild-type or] mutant retroviral oncogene DNA; or

(2) [wild-type or] mutant proto-oncogene DNA of a species different from the host species.

3. (once amended) [An] A cellular immunogen [according to claim 2] for immunizing a host against the effects of the product of a target proto-oncogene, the overexpression of which target proto-oncogene is associated with a cancer, which cellular immunogen comprises allogeneic donor cells which have been transfected with at least one transgene construct comprising at least one transgene cognate to the target proto-oncogene and a strong promoter to drive the expression of the transgene in the transfected cells, the transgene encoding a gene product which induces host immunoreactivity to host self-determinants of the product of the target proto-oncogene gene, and wherein the transfected cells are non-dividing.

4. (once amended) An immunogen according to claim [2] 3 wherein the transgene comprises mutant retroviral oncogene DNA or mutant proto-oncogene DNA.

6. (once amended) An immunogen according to claim [5] 2 wherein the mutant DNA comprises a deletion mutation in a region of said DNA which is essential for transformation.

10. (once amended) A method for preparing a cellular immunogen for immunizing a host against the effects of the product of a target proto-oncogene, the overexpression of which target proto-oncogene is associated with a cancer, the method comprising:

transfecting allogeneic donor cells with at least one transgene construct comprising at least one transgene cognate to the target proto-oncogene and a strong promoter to drive the expression of the transgene in the transfected cells, wherein the transgene is non-transforming and encodes [encoding] a gene product which induces host immunoreactivity to host self-determinants of the product of the target proto-oncogene gene.

11. (once amended) A method according to claim [11] 10, wherein the transgene comprises:

(1) [wild-type or] mutant retroviral oncogene DNA; or

(2) [wild-type or] mutant proto-oncogene DNA of a species different from the host species.

12. (once amended) A method [according to claim 11] for preparing a cellular immunogen for immunizing a host against the effects of the product of a target proto-oncogene, the overexpression of which target proto-oncogene is associated with a cancer, the method comprising:

transfecting allogeneic donor cells with at least one transgene construct comprising at least one transgene cognate to the target proto-oncogene and a strong promoter to drive the expression of the transgene in the transfected cells, the transgene encoding a gene product which induces host immunoreactivity to host self-determinants of the product of the target proto-oncogene gene, wherein the transfected cells are non-dividing.

13. (once amended) A method according to claim [11] 12 wherein the transgene comprises mutant retroviral oncogene DNA or mutant proto-oncogene DNA.

15. (once amended) A method according to claim [14] 11 wherein the mutant DNA comprises a deletion mutation in a region of said DNA which is essential for transformation

17. A method according to claim [11] 10 wherein the transgene is cognate to a target proto-oncogene selected from the group of proto-oncogenes consisting of AKT-2, c-*erbB*-2, MDM-2, c-*myc*, c-*myb*, c-*ras*, c-*src* and c-*yes*.

18. (once amended) A method according to claim [1] 10, wherein the donor cells comprise fibroblasts or bone marrow-derived antigen-presenting cells.

27. (once amended) A method according to claim 19 wherein the donor host cells comprise fibroblasts or bone marrow-derived antigen-presenting cells.[.]

28. (once amended) A method of vaccinating a host against a disease associated with the overexpression of a targeted proto-oncogene comprising

(a) transfecting allogeneic donor cells with at least one transgene construct comprising at least one transgene and a strong promoter to drive the expression of the transgene in the transfected cells, wherein the transgene comprises:

(1) wild-type or mutant cognate retroviral oncogene DNA; or

(2) wild-type or mutant cognate proto-oncogene DNA of a species different from the host species; and

(b) inserting the cells transfected with the transgene construct into the body of the host to obtain expression of the transgene in the host.